journal of clinical practice 2021 Vol 12 №2

POST-COVID-19 NEUROLOGICAL SYNDROMES

V.V. Belopasov[1], E.N. Zhuravleva[2], N.P. Nugmanova[1], A.T. Abdzashitova[1]

[1] Astrakhan State Medical University, Astrakhan, Russian Federation

[2] Regional Clinical Hospital, Astrakhan, Russian Federation

The article covers the pathogenesis and clinical manifestations of the damage to the central and peripheral nervous systems in COVID-19 patients, which appeared or remained in the post-COVID-19 period (Long-COVID-19). Their correct assessment, application of efficient approaches to the complex treatment and targeted neurorehabilitation provide a reversible character of the functional impairment, prevention or reduction of disability, improvement of the quality of life, prevent the progression of cognitive, emotional, behavioral disorders initiated by SARS-CoV-2.

Keywords: *subacute; chronic COVID-19; diseases of central and peripheral nervous system.*

For citation: Belopasov VV, Zhuravleva EN, Nugmanova NP, Abdzashitova AT. Post-COVID-19 Neurological Syndromes. *Journal of Clinical Practice.* 2021;12(2):69–82. doi: https://doi.org/10.17816/clinpract71137

Submitted 25.05.2021 Revised 02.06.2021 Published 30.06.2021

List of abbreviations

CT — computed tomography
CPK — creatine phosphokinase
MRI — magnetic resonance imaging
PET — positron emission tomography
COVID-19 (COronaVIrus Disease 2019) — coronavirus infection of 2019
SARS-CoV-2 — a novel severe acute respiratory syndrome-related coronavirus 2

BACKGROUND

Awareness of clinical forms, their combinations, diagnostic algorithms, and methods of objective assessment, characteristic of the post-COVID period of functional and structural changes in the brain, autonomic and peripheral nervous system, is important not only for making a diagnosis, choosing pharmacotherapy and methods of neurorehabilitation, but also for predicting the results, substantiation of prophylactic measures to prevent the negative impact of the disease on the physical, social, and mental well-being of the patient, prevent negative outcomes in the form of loss of labour capacity, disability, and delayed long-term consequences of coronavirus infection (chronic angioencephalopathy, structural epilepsy, parkinsonism, leucoencephalopathy, and other progressive forms of neurodegenerative and autoimmune pathology).

During the ongoing COVID-19 pandemic, the assessment by the attending physician (neurologist, physiotherapist, rehabilitation therapist, psychotherapist) of a patient who has had COVID-19 is determined by his health condition at the time of seeking medical help, the presence of clinical manifestations and complications identified in him in the acute phase, the success of the therapy, as well as the continuing consequences of the disease that affect negatively the quality of life. Hans Kluge, Head of the European Regional Office of the World Health Organization, commented: “We have passed the worst case scenario. We know more about the coronavirus compared to 2020, when it just began to spread.” The mechanisms of invasion and clinical manifestations of SARS-CoV-2 before entering and during the patient’s stay in the hospital are mainly characterized [1–5], and those that arise and persist during treatment at home, as well as after discharge from the infectious diseases department for follow-up treatment and rehabilitation, require comprehension.

In our review, we will focus on neurological complications and psychosomatic disorders in the post-COVID period, which doctors register at outpatient visits and in hospitals.

Already in the first months after the announcement by the World Health Organization of the onset of a pandemic and the need to manage its consequences [6], during the functional assessment of the condition of patients at all stages of the disease, the time periods for the onset and maintenance of clinical symptoms were outlined, which reflected its severity and localiza-

tion depending on the damage of organ or organs and target systems; and the types and subtypes of long COVID syndrome have been developed and subsequently refined [7, 8]:

- type 1 (acute COVID-19) is characterized by the development of poorly or insufficiently curable deficient structural disorders during the period of infection of the patient;
- type 2 is characterized by ongoing symptomatic course for 4–12 weeks after being infected with COVID-19;
- type 3 (long COVID, long haulers, longhaul COVID-19 syndrome, more than 12 weeks) is characterized by continuous, relapsing, remitting course (≥ 3 months for *subtype 3A*, ≥ 6 months for *subtype 3B*) after almost complete recovery or reduction of the initial symptoms;
- type 4 is characterized by in the asymptomatic course of the acute period, and sudden development of organ pathology after 1–3 months (*subtype 4A*) or more (*subtype 4B*);
- the type 5 is characterized by a lethal outcome causally associated with a latent disease of the lungs, myocardium, and vessels supplying them and the brain [9, 10].

This approach enables to diagnose, treat, and rehabilitate patients, regardless of their age, outside COVID hospitals. Persistent or re-emerging symptoms, functional disorders associated with COVID-19, in ≥50% of cases, according to the questionnaire survey and analysis of the disease outcomes in hospitals and clinics, affect negatively the quality of life, mobility, and independence of patients seeking medical help [11–14].

Symptoms requiring the attention of a neurologist include re-emerging or persisting local pain; tachycardia; unproductive, heavy cough uncontrollable by broncho- and mucolytics; periodic drop in the level of saturation with pulse oximetry; dyspnea; paresthesia; diplopia; hiccups; decrease/loss of sense of smell, taste, vision, hearing; fatigue; dizziness; poor exercise tolerance; loss of appetite or muscle mass; sudden "shutdown" of consciousness; focal and generalized seizures; changes in mood, speech, gait; disorder of swallowing, coordination, memory, behavior, sleep, thermoregulation; the presence or progression of asthenia, and numbness in the extremities [15, 16].

Cephalalgia. Its main types, with the exclusion of "red" and "orange flags" [17], are episodic or permanent tension headache; cough headache arising during physical and cognitive stress; compression/ischemic (from compression of the pericranial muscles, scalp, soft tissues, blood vessels with protective helmets, masks, glasses) secondary headache (with inflammation of the paranasal sinuses, meningoencephalitis, diffuse leukoencephalopathy, vasculitis, epidural hematoma, cerebral apoplexy, thrombosis of the sinuses and veins, hemorrhage in the pituitary gland, intracranial hypertension, hypoxia, hypercapnia, cerebral edema) [18, 19], as well as new (previously absent), pulsating or pressing, moderate to severe, holocranial, prolonged (more than 72 hours), migraine-like headache associated with activation of the trigeminovascular system, resistant to standard therapy, associated with systemic viral infection (lung damage, elevated blood levels of D-dimer, IL-6, TNF-α, thrombocytopenia, lymphopenia, hyperferritinemia) [20–22]. Changes in the frequency or severity of attacks, increase in doses of drugs compared to the period before the pandemic, transformation into a chronic form take place in the presence of migraine in patients prior to infection with SARS-CoV-2 [23]. An aspect of post-COVID migraine-like cephalalgia is its persistence for more than 6 weeks with the disappearance of other symptoms of COVID-19 [24, 25]. The development of pseudomigraine, orofacial, temporomandibular, and masticatory pain is usually associated with psychogenic stress or local myositis [26, 27].

Craniopathy. Disorders of smell, taste, vision, and hearing with the onset in the acute period of the disease are most often reversible within the first 3 weeks [4, 28, 29]. The absence or partial restoration of the sensory system is noted in inflammatory neuropathies of cranial nerves I, II, IV, VII, VIII [30–34], iatrogenic damage to the nerves X, XII (Tapia syndrome) after tracheal intubation [35]. Involvement of nerves II, III, V, VI in the pathological process is possible with thrombosis of the cavernous sinus [36], and that of nerves III, VII, IX, X, XII is possible with stem stroke (own case; Fig. 1), autoimmune complications (Guillain-Barré syndrome, Miller Fisher syndrome) [37, 38], involvement of nerve X is possible in sensory laryngeal neuropathy (SLN) [39], postviral vagal neuropathy (PVVN), clinically manifested in the form of persistent, therapy-tolerant cough arrested by the intake of amitriptyline, gabapentin [40, 41].

Autoimmune complications are inflammatory demyelinating polyradiculoneuropathies (Guillain-Barré syndrome, Miller Fisher syndrome), leukoencephalopathy, autoimmune encephalitis, Bickerstaff rhombencephalitis, limbic encephalitis, anti-NMDAR encephalitis, acute disseminated encephalomyelitis, transverse/longitudinal myelitis, opticomyelitis,

https://doi.org/10.17816/clinpract71137

journal of clinical practice 2021 Vol 12 №2

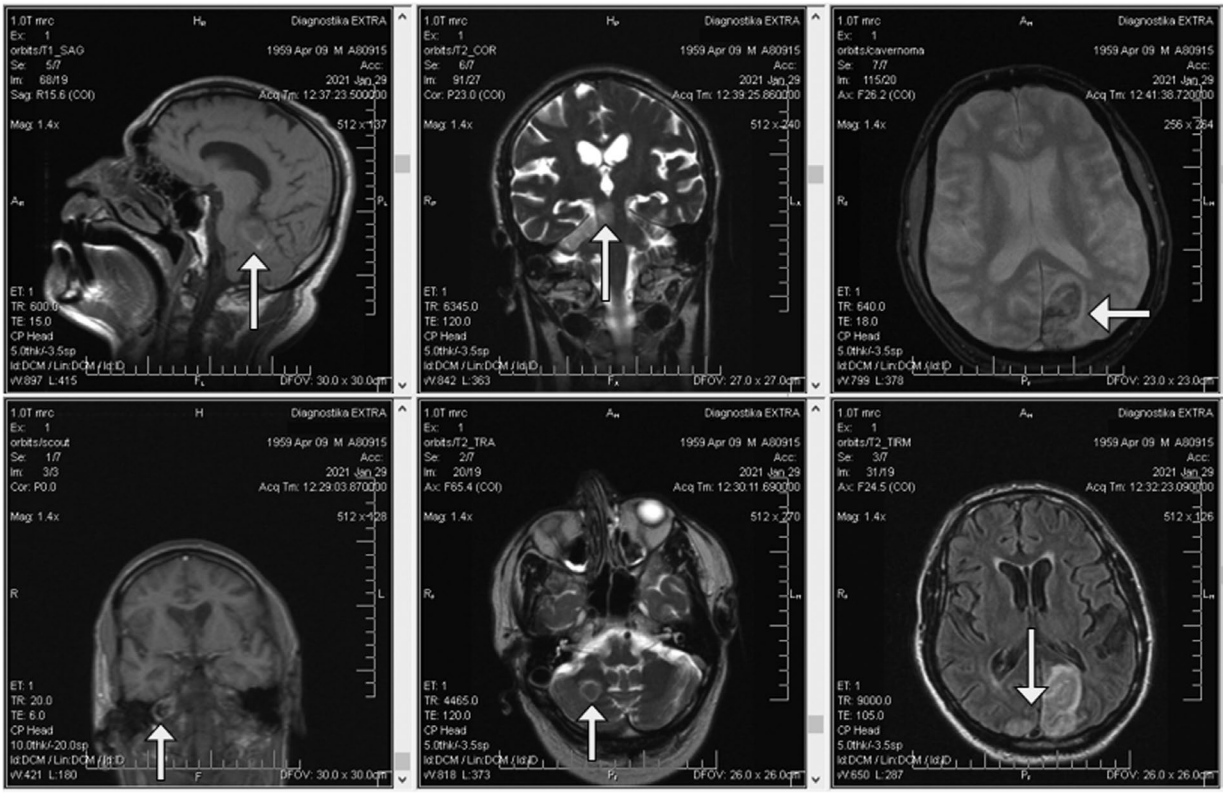

Fig. 1. Arterio-arterial cerebral embolism of basial artery branches. Right-side hemi-syndrome of the brainstem, cerebellum. Asymmetric infarctions of occipital lobes.

multiple sclerosis, myasthenia gravis *de novo*, multiple mononeuritis, and cervicobrachial plexopathy [4, 42–45]. Some of these forms debut in the post-COVID period [46, 47], one of the dramatic complications of which is Graves' malignant edematous exophthalmos (autoimmune thyroiditis) (own case, Fig. 2). There have also been isolated cases of post-vaccination transverse myelitis, the development of Guillain-Barré syndrome after COVID-19 vaccination with Pfizer [48, 49], but the number of patients with post-vaccination immune-mediated complications should not increase, since there is no evidence of a causal relationship between their development and vaccination against COVID-19.

Deficient forms of damage to the nervous system that persist in the early recovery period. Patients with partially recovered or persisting speech, motor, sensory, autonomic, mental, and cognitive impairments need to continue personalized treatment and conduct rehabilitation measures using a multidisciplinary approach, traditional and new technologies during the first 6 months after discharge from the hospital. Methods and scope of treatment are determined by nosology and forms of neurological complications

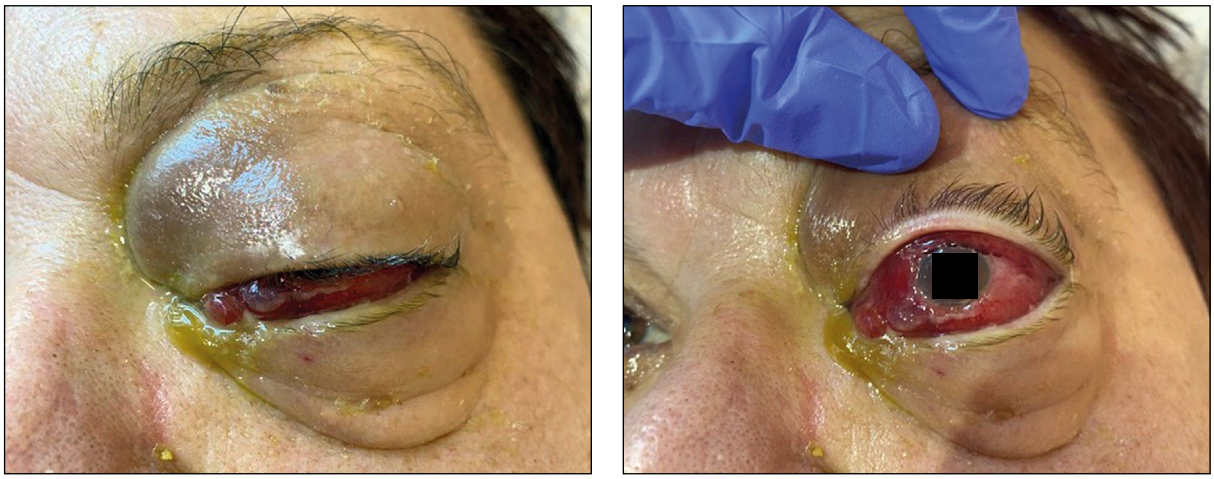

Fig. 2. Malignant edematous Graves' exophthalmos. Chemosis, ophthalmoplegia.

such as meningoencephalitis; encephalitis; leukoencephalitis; Parkinson's syndrome, locked-in-syndrome; cerebellitis; Bickerstaff rhombencephalitis; leukoencephalopathy; encephalopathy of critical conditions; thrombosis of the cerebral sinuses and cerebral veins; ischemic, hemorrhagic strokes; spinal stroke; encephalomyelitis; myelitis; opticomyelitis; plexopathy; mono-, multi-, polyneuropathy; neuromyopathy; myasthenia gravis [4, 50–52].

Thoracalgia (muscle-tonic, myofascial, visceregenic) occurs with pleuritis, pulmonary fibrosis; cough; breathing (at rest, during physical exertion); hyperventilation; spasm of greater, smaller pectoral, serratus anterior, and trapezius muscles; sternal syndrome (angina pectoris, myocardial infarction) in 64% of patients in the acute period and in 31% in the recovery period [53, 54]; with chronic fatigue syndrome; in isolated cases with myocarditis, cardiomyopathy, pericarditis, aortitis, dissection of the aorta, thrombosis of the aorta, pulmonary artery and its branches, fractured ribs with cough, pneumothorax, pneumomediastinum, mediastinal emphysema, rupture of the diaphragm, intercostal pneumocele, penetration of the stomach and small intestine into the chest cavity [55, 56].

Abdominalgia. Its emergence in the presence or absence of respiratory symptoms may be associated with a spasm of the abdominal muscles; cough hernia of the abdomen; intestinal dyskinesia; the development of pneumoperitoneum, pancreatitis, hepatitis, acute liver failure, drug-induced gastroenteritis, colitis; exacerbation of comorbid forms of gastrointestinal diseases in patients; dissection of the aorta; aortitis [57–59]; thrombosis of the mesenteric and splenic arteries or their branches [60, own case].

Neuropathic post-COVID pain (acute and chronic) occurs during inflammation, ischemia, compression damage to peripheral nerves, plexuses, activation of neurons in the posterior horns of the spinal cord, autonomic fibers of the sympathetic nervous system, as well as involvement of the thalamus and somatosensory cortex in the pathological process [61, 62]. The main cohort is represented by patients discharged for follow-up care and rehabilitation after intensive care in a COVID hospital (post-intensive care syndrome, critical illness neuropathy and polyneuropathy, CIN). Compression of peripheral nerves and their branches (nerve entrapment sensory neuropathy, NESN) on the upper and lower extremities in moderate to severe acute respiratory distress syndrome is possible in the prone position. Symptoms typical for neuropathic pain (the presence of paresthesias, hyperpathia, allodynia, signs of autonomic dysfunction) are typical of postherpetic neuralgia, diabetic painful neuropathy, notalgia paresthetica (damage to the paravertebral posterior branches of the spinal nerves and ganglia), sensory peripheral neuropathies, Parsonage-Turner sensory amyotrophic neuralgia, axonal and demyelinating variants of inflammatory and parainfectious polyradiculoneuropathies [63–65]. The development of central post-stroke pain is caused by damage to the thalamus, brain stem, and spinothalamic tracts [66, 67].

Lesions of the peripheral nervous system are manifested in the form of mononeuropathies, multiple neuropathies, polyneuropathies, plexopathies, polyradiculoneuropathies, in the genesis of which, in addition to inflammation and compression [68, 69], a significant role is played by molecular mimicry between viral proteins and peripheral nerve proteins (GM1, GD1a, GT1a, GQ1b) [70, 71].

Post-COVID epileptic seizures. Carriage of the virus, its penetration into the neurons of the cerebral cortex does not initiate the epileptiform activity, and does not affect the clinical characteristics and frequency of seizures in COVID-19 patients. Structural and functional disorganization in the lesion focus, caused by an inflammatory, autoimmune process, and cerebral ischemia in the acute stage of the disease provoked by SARS-CoV-2, is important, but not decisive for the epilepticization of neurons [72, 73]. In the post-COVID period, epileptic seizures can occur and proceed severely (serially in the form of non-convulsive and convulsive epileptic status, as bilateral tonic-clonic, myoclonic seizures or, extremely rarely, opsoclonus-myoclonus) not only in patients with epilepsy [74, 75]. Their development is possible to be associated with structural changes of a different etiology that have not been identified in the premorbid period (atrophy, hippocampal sclerosis, developmental anomalies, malformations, brain trauma) [73].

Chronic fatigue syndrome (CFS), also called Iceland disease; myalgic encephalomyelitis (ME); epidemic neuromyasthenia gravis; post-viral asthenia syndrome; post-active phase of infectious syndromes (PAPIS); chronic fatigue syndrome and immune dysfunction (CFIDS), systemic exertion intolerance disease (SEID). Clinical manifestations are characterized by varying degrees of severity, protracted or undulating course. The main negative signs, such as dyspnea, poor tolerance or inability to perform physical and cognitive loads, fatigue that does not disappear after rest, post-exertional malaise (PEM), muscle pain/myalgia of various localization, persist for at least 6

https://doi.org/10.17816/clinpract71137

journal of clinical practice 2021 Vol 12 №2

months after a viral infection that initiates the production of cytotoxins, proinflammatory cytokines, and autoantibodies against key enzymes that ensure the functioning of mitochondria and self-regulation of energy metabolism [76, 77]. Influenza viruses, herpes simplex types I, II, VI, Epstein-Barr virus, cytomegalovirus, hepatitis C, and since 2020 SARS-CoV-2, are classified as causative viruses [78, 79]. Accompanying symptoms include subfebrile condition; episodes of fever, hyperhidrosis; lymphadenopathy; lymphocytopenia; persistent cough, persistent shortness of breath; decrease in SpO_2 during exercise; tightness in the chest; muscle weakness; paresthesia; migratory arthralgias; fibromyalgia; headache; poor tolerance to light or noise; nonsystemic dizziness; brain fog; syncope-like paroxysms; postural fulminant orthostatic hypotension; tachycardia; dysphoria; sensory-perceptual, somatized, communication, behavioral, or affective disorders; sexual dysfunction; disorders of falling asleep, sleep, memory, attention, and comprehension [80, 81]. These complications are noted in 30–50% of convalescents, more often in women than in men and children; their severity and persistence is higher in patients treated in intensive care units and resuscitation departments, with multiple organ and comorbid forms of pathology [82, 83]. The continuing negative changes in physical and social functioning affect negatively the quality of life, and assessment of the ongoing drug therapy and rehabilitation of patients [84].

Cognitive impairments. Their development and progression are based on persistent hypoperfusion of the brain; metabolic disorders; virus-induced structural damage to neurons (areas of the brain that provide fixation and preservation of memory are affected in a varying degree, namely the cortex of the temporal and occipital lobes, hippocampus, amygdaloid body, thalamus, and cerebellum); secondary impairment of the functioning of neurochemical mechanisms of perception, understanding, consolidation of information required for the provision of mental and intellectual activity of an individual [85, 86]. Patients with a neurocognitive defect complain about memory problems (assimilation of new information, understanding, reproduction of what was seen, heard, or read), performing daily activities, communication with others. When assessing neuropsychological testing and motor activity, defects in communication, attention, recognition, understanding, thinking, motor skills, memorization, and reproduction of a number of words, numbers, and figures are revealed. Adaptive behavior, performance, cognitive activity, comprehension, episodic, procedural, semantic, operational, fixation, short-term memory, as well as financial management, and family relationships are affected [87, 88]. Cognitive impairment is not associated with drug intake, critical self-esteem of cognitive potential is maintained, and the degree of decline is within the range from mild to moderate impairment [89, 90]. When the markers of the neurodegenerative process are detected on the magnetic resonance imaging (MRI) and in the cerebrospinal fluid, the changes in the cognitive sphere are non-dement [91, 92]; while the presence and replication of coronavirus in the structures and organelles of the brain, the smoldering inflammatory process that stimulates the deposition of beta-amyloid and tau protein in neurons of the temporal lobe, are significant factors in the development of Alzheimer's disease in patients with the history of COVID-19, and its progression in patients with existing COVID-19 [93, 94].

Mental and behavioral disorders are an integral part of the post-COVID tail [95, 96]. The memory of the illness, its manifestations, fear of death, the possibility of a relapse of the disease, incomplete recovery of physical and mental health, awareness of full or partial dependence on others become the cause of their development, regardless of where and how the patient was treated (in the resuscitation department, intensive care unit, on an outpatient basis, or independently). Preservation and aggravation of somatic ill-being, the emergence of new symptoms, dissatisfaction with the quality of the therapy, and insecurity give rise a maladaptive response of the neurotic and affective register, depending on the type of personality, self-esteem, the degree of compliance and the significance of a particular social trigger [97, 98]. The main clinical forms include psychological distress; post-traumatic stress disorder; asthenia; dysthymia; anhedonia; hypochondria; phobia; anxiety; panic attacks or their subtypes; generalized anxiety disorder; catastrophizing; obsessive states; depression; Alan Baddeley dysexecutive syndrome (DES) as the loss of control over behavior in presence of cognitive and emotional impairments [99–101]. Emotional instability manifests itself in the form of mood swings, dysphoria, irritability, tearfulness, verbal and physical aggression. Behavioural disorders are clinically and prognostically equally significant. Patients are apathetic, hypodynamic, prefer bed rest, self-isolation; their communication with relatives, friends, and work colleagues is disrupted; they have impaired executive functions, decreased appetite, mental, physical, and sexual activity. Attention is focused on somatovisceral manifestations and their change over time. Some patients experience persistent

unpleasant olfactory hallucinations (parosmia, phantosmia) [102, 103]. Attempts by relatives and a doctor to influence the patient's self-esteem provoke psychotic reactions, explosive behavior, conversion disorders, and suicide. A negative contribution to their development is made by the determined (by MRI, PET) damage by the virus of the zones functionally significant for the affect implementation in the anterior parts of the frontal and temporal lobes of the brain [104, 105].

Autonomic dysfunction manifests itself in fluctuations in the level of blood pressure (BP) and heart rate at rest, with verticalization, low physical exertion, forced exhalation with closed nose and mouth, breath holding with sharp straining (Valsalva test) [106, 107]. When performing ortho- and clinostatic tests, postural orthostatic hypotension and orthostatic tachycardia without hypotension (postural tachycardia syndrome, POTS) are detected [108, 109]. In the supine position (in 41% of patients) and in upright position (in 72%), the patients have a sensation of "falling down", nonsystemic dizziness [110]; as well as a high probability of arrhythmias [111, 112], vasodepressor [113, 114] or reflex syncope (nocturic, during defecation) [115], Takotsubo cardiomyopathy as reversible dyskinesia of the left ventricle of the heart threatening the patient's life associated with catecholaminemia, and stress hyperactivity of sympathetic nervous system [116, 117]. Another clinical phenomenon which requires attention is the platypnea-orthodeoxia syndrome (POS). The patients seek medical help due to the positional dyspnea (tachypnea) in verticalization, which causes panic; in a horizontal position, the patient's condition is normal [118, 119]. Similar symptoms occur during any physical activity accompanied by brain hypoperfusion [106, 110, 120]. At the time of the onset of paroxysm, a situational drop in saturation in the range of 8–12% is recorded. The main contingent is represented by patients with the history of acute respiratory distress syndrome [118].

The basic signs of **autoimmune autonomic ganglionopathy, upper and lower brainstem and endocrine dysfunction**, in addition to those indicated, include disorders of thermoregulation (sudden daily temperature fluctuations in the form of hyper-/hypothermia, poor cold/heat tolerance, poikilothermia), sleep (insomnia); spontaneously occurring episodes of dyspnea, excessive sweating; vegetative (cardiac, abdominal, dysuric) paroxysms; cough/vasovagal syncope (bettolepsy, respiratory seizure); Reynaud's syndrome; irritable bowel syndrome; loss of appetite; anorexia; asthenodynamia/exhaustion; dysmenorrhea; libido; secondary (central) hypo- and hyperthyroidism; Graves' disease (malignant exophthalmos); hypocorticism (adrenal insufficiency); syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [121–123]. Neurophthalmic autonomic syndromes (Horner, Adie – Holmes) develop extremely rarely [124, 125].

Neurotrophic and metabolic disorders attract attention not only in the acute, but also in the post-COVID period. Their development is associated with the neurotropic, inflammatory potential of SARS-CoV-2, reactivation of *Herpes zoster*, prolonged immobilization of the patient, local tissue ischemia, diabetes mellitus, sensory, autonomic neuropathy, prolonged use of antihypertensive, sedative drugs, vasopressors, muscle relaxants, and corticosteroids [126, 127]. Clinically significant manifestations include Melkersson–Rosenthal syndrome [128]; periorbital edema; cellulitis; orbital cellulitis; necrosis; perforation of the hard palate [129]; ectasia of the salivary glands; dry mouth (xerostomia) [130], xerosis, dry cornea of the eyes (xerophthalmia, dry eye syndrome) [131]; hair loss/alopecia [132]; heterotopic ossification [133]; decrease in bone mineral density; osteoporosis; osteosclerosis; osteonecrosis of the talus, calcaneus, humerus, or femur [134]; "frostbitten" fingers, COVID toes/pseudo-chilblain [135]; typical and atypical bedsores (localization in the face, anterior chest wall, abdomen, iliac crests, knees) [136, 137]; ulcers of the mucous membranes of the lips, cheeks, gums, oral cavity, hard palate, and tongue [138].

Muscle lesion (myalgia, myopathy, myasthenic syndrome). The development and subacute course of the inflammatory process, infection of muscle cells expressing receptors of angiotensin-converting enzyme 2, as well as prolonged immobilization, ventilation of the lungs with the use of muscle relaxants, the use of chloroquine, hydroxychloroquine, ribavirin, and corticosteroids cause the development and persistence of local edema in patients, muscle induration, muscle weakness, fatigue, myalgia, dyspnea, and weight loss (decrease in muscle mass). In-depth instrumental (electromyography, MRI, ultrasound examination of the muscles of the upper and lower extremities, heart, diaphragm, phrenic nerve in the neck, intercostal muscles, muscles of the upper and lower extremities) and laboratory (determination of the blood levels of pro-inflammatory cytokines, CPK, myoglobin) examinations, as well as study of muscle tissue during biopsy and autopsy reveal in patients reliable signs of damage to the neuromuscular apparatus in the form of flaccid tetraparesis/tetraplegia; dysphagia; myasthenic muscle fatigue; sarcopenia (myopenia); inflammatory myopathy; cardiomyopathy; myositis; muscle necrosis (rhab-

https://doi.org/10.17816/clinpract71137

journal of clinical practice 2021 Vol 12 №2

domyolysis); atrophy of the muscles of the diaphragm, intercostal muscles, abdomen, skeletal muscles; dysfunction; hypertrophy; fibrosis of the muscles of the diaphragm during artificial pulmonary ventilation; an increase in the blood levels of total and MB-fraction of CPK [139, 140]. Attention is drawn to the heterogeneity of clinical forms. Critical illness myopathy (CIM) ranks first; other variants arising in the acute and post-COVID period are rare, these include paraspinal COVID-myositis of the lumbar muscles and pelvic girdle, faciobulbar limb form; post-vaccination COVID-myositis; inflammatory and immune myopathies (IIM), myositis, dermatomyositis; generalized, local myasthenia gravis *de novo* [141, 142]; some of them (rhabdomyolysis, dermatomyositis with antibodies to MDA5, necrotizing autoimmune myositis/NAM/anti-HMGCR myopathy subtype IIM) can be fatal [143, 144]. Differential diagnostics enables to rule out idiopathic inflammatory myopathies, statin-associated autoimmune myopathy, dermatomyositis, poliomyositis in connective tissue diseases; anti-SS-OM myositis, secondary neurogenic forms of muscle damage in positional compression neuropathy; phrenic neuropathy in diabetes mellitus, alimentary insufficiency, inflammatory autoimmune, drug-induced forms of polyneuropathy, sensomotor axonal polyneuropathy of critical conditions (critical illness polyneuropathy, CIP), polyneuropathy-myopathy (CIPM, CINM) [145, 146]. Intensive care unit acquired limb and trunk weakness (ICUAW) is common but rare [147]. Early recognition, definition of complication nosology, knowledge of the pathogenesis and course of the pathological process allow timely prescribing and conducting personalized therapy and rehabilitation, minimizing the development of negative functional consequences in a particular patient.

Dysfunction of the basal ganglia, nigrostriatal system, and cerebellum. Dysfunction of the basal ganglia is a rare form of damage to the nervous system in COVID-19. It is associated with intracerebral hemorrhages, neuroinflammation as a necrotic form of hemorrhagic leukoencephalopathy, cerebral infarctions, deep cerebral vein thrombosis caused by arteritis/endotheliitis, hypercoagulation of subcortical vessels, multilevel damage (cortical and subcortical segments, upper and medial segments of the trunk, cerebellum), the causes of which include also parainfectious autoimmune, toxic-hypoxic and drug-induced brain lesions [148, 149]. The niveau diagnosis, when neuroimaging is impossible, is based on the assessment of motor manifestations. These include hand tremor, myoclonus of the soft palate, cerebellar ataxia, catatonia, akathisia, akinetic-rigid syndrome, akinetic mutism, locked-in syndrome, choreic hyperkinesis, generalized and local myoclonus, and opsoclonus-myoclonus [150–152]. In the post-COVID period, the retaining of neuroinflammation, oxidative distress in these patients, as well as the accumulation of alpha-synuclein in the brain structures, and the induction of local autoimmune reactions are important conditions for the development and progression of the neurodegenerative process after neuroinvasion [153, 154]. The destructive effect of COVID-19 is especially pronounced in patients with Parkinson's and Alzheimer's diseases [155, 156]. The mortality rate is higher in case of Alzheimer's disease [157].

Drug-induced complications. Drugs used in the treatment of COVID-19 patients can cause the development of paresthesias (lopinavir/ritonavir), headache (azithromycin, tocilizumab), myalgia, myositis, toxic myopathy, rhabdomyolysis (chloroquine, hydroxychloroquine, azithromycin, colchicine, linezolid, corticosteroids), neuromyopathy (chloroquine, hydroxychloroquine), visual and hearing impairment (chloroquine, hydroxychloroquine), dizziness, ataxia (azithromycin, hydroxychloroquine, umifenovir/arbidol), drug-induced arrhythmias, hypotension, fainting, seizures, cardiac arrest (chloroquine, hydroxychloroquine, remdesivir, azithromycin), cerebral thrombotic microangiopathy, leukoencephalopathy (tocilizumab) [158–161]. Some drugs cause emotional disorders (chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, corticosteroids, interferon α2b), sleep disorders (azithromycin, interferon α2b) [158]. Corticosteroids, tocilizumab, and interferon α2b have a negative effect on cognitive and executive functions [160]. Abnormal behavior, delirium, exaltation, and hallucinations are provoked by chloroquine, hydroxychloroquine, corticosteroids, lopinavir/ritonavir, interferon α2b, umifenovir/arbidol, and favipiravir [158, 160].

The lethal outcome, intracerebral hemorrhage, ischemic stroke, thrombosis of the cerebral sinuses and veins with/without thrombocytopenia, Bell's palsy, dysphonia, tremor, acute transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and focal epileptic seizures *de novo* were registered in administration of AstraZeneca, Pfizer, Moderna, Janssen, Covaxin vaccines [162–165], however these complications, even given their tragic nature, do not occur more often than in the vaccine prophylaxis of other infections. The benefits of vaccination at the population level far outweigh the risks of neurological complications. Anti-COVID vaccines are most proba-

bly a provoking factor, a trigger, but not a cause of their development.

CONCLUSION

Thus, the main target of SARS-CoV-2 is the respiratory tract, but its next targets are the brain, muscle and immune systems. Neurological complications such as acute cerebrovascular failure, impaired consciousness, and skeletal muscle damage develop most probably in patients with severe infection course. Involvement of the central nervous system in the pathological process is a predictor of a poor prognosis. In such patients, the condition can deteriorate quickly and lethal outcome can occur. When assessing clinically the condition of patients, doctors, regardless of their specialty, need to pay close attention not only to the respiratory manifestations of the disease, but also to neurological symptoms, the presence and progression of which is possible both in the acute and post-acute periods (COVID-19 Long Tail).

ADDITIONAL INFORMATION

Author contribution. Belopasov V.V. — concept of the review, literature analysis, manuscript editing, Zhuravleva E.N., Nugmanova N.P., Abdzashitova A.T. — consult of the patient, illustrations. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

REFERENCES

1. Yachou Y, El Idrissi A, Belopasov V, Benali SA. Neuroinvasion, neurotropic and neuroinflam-matory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. *Neurol Sci*. 2020;41(10):2657–2669. doi: 10.1007/s10072-020-04575-3

2. McGowan EM, Haddadi N, Nassif NT, Lin Y. Targeting the SphK-S1P-SIPR Pathway as a Potential Therapeutic Approach for COVID-19. *Int J Mol Sci*. 2020;21(19):7189. doi: 10.3390/ijms21197189

3. Baklaushev VP, Kulemzin SV, Gorchakov AA, et al. COVID-19. Etiology, pathogenesis, diagnosis and treatment. *Journal of Clinical Practice*. 2020;11(1):7–20. (In Russ). doi: 10.17816/clinpract26339

4. Belopasov VV, Yashu Ya, Samoilova EM, Baklaushev VP. Lesion of the nervous system in COVID-19. *Journal of Clinical Practice*. 2020;11(2):60–80. (In Russ). doi: 10.17816/clinpract34851

5. Reza-Zaldívar EE, Hernández-Sapiéns MA, Minjarez B, et al. Infection Mechanism of SARS-COV-2 and Its Implication on the Nervous System. *Front Immunol*. 2021;11:621735. doi: 10.3389/fimmu.2020.621735

6. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (UK); 2020.

7. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020;81(6):e4–e6. doi: 10.1016/j.jinf.2020.08.029

8. Yong SJ. Persistent brainstem dysfunction in long-COVID: a hypothesis. *ACS Chem Neurosci*. 2021;12(4):573–580. doi: 10.1021/acschemneuro.0c00793

9. Taboada M, Cariñena A, Moreno E, et al. Post-COVID-19 functional status six-months after hospitalization. *J Infect*. 2021;82(4):e31–e33. doi: 10.1016/j.jinf.2020.12.022

10. Oronsky B, Larson C, Hammond TC, et al. A review of persistent post-COVID syndrome (PPCS). *Clin Rev Allergy Immunol*. 2021;1–9. doi: 10.1007/s12016-021-08848-3

11. Garg P, Arora U, Kumar A, Wig N. The «post-COVID» syndrome: how deep is the damage? *J Med Virol*. 2021;93(2):673–674. doi: 10.1002/jmv.26465

12. Iqbal A, Iqbal K, Arshad AS, et al. The COVID-19 sequelae: a cross-sectional evaluation of post-recovery symptoms and the need for rehabilitation of COVID-19 survivors. *Cureus*. 2021;13(2):e13080. doi: 10.7759/cureus.13080

13. Moreno-Pérez O, Merino E, Leon-Ramirez JM, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a mediterranean cohort study. *J Infect*. 2021;82(3):378–383. doi: 10.1016/j.jinf.2021.01.004

14. Wijeratne T, Crewther S. COVID-19 and long-term neurological problems: Challenges ahead with Post-COVID-19 Neurological Syndrome. *Aust J Gen Pract*. 2021;(50). doi: 10.31128/AJGP-COVID-43

15. Seyed AS, Afsahi AM, Mohsseni PM, et al. Late complications of COVID-19; a systematic review of current evidence. *Arch Acad Emerg Med*. 2021;9(1):e14. doi: 10.22037/aaem.v9i1.1058

16. Nuzzo D, Cambula G, Bacile I, et al. Long-term brain disorders in post COVID-19 neurological syndrome (PCNS) patient. *Brain Sci*. 2021;11(4):454. doi: 10.3390/brainsci11040454

17. García-Azorín D, Trigo J, Talavera B, et al. Frequency and type of red flags in patients with COVID-19 and headache: a series of 104 hospitalized patients. *Headache*. 2020;60(8):1664–1672. doi: 10.1111/head.13927

18. Bobker SM, Robbins MS. COVID19 and headache: a primer for trainees. Headache. *J Head Face Pain*. 2020;60(8):1806–1811. doi: 10.1111/head.13884

19. Silva MT, Lima MA, Torezani G, et al. Isolated intracranial hypertension associated with COVID-19. *Cephalalgia*. 2020;40(13):1452–1458. doi: 10.1177/ 0333102420965-963

20. Toptan T, Aktan C, Basar A, Bolay H. Case series of headache characteristics in COVID-19: headache can be an isolated symptom. *Headache*. 2020;60(8):1788–1792. doi: 10.1111/head.13940

21. Karadaş Ö, Öztürk B, Sonkaya AR, et al. Latent class cluster analysis identified hidden headache phenotypes in COVID-19: impact of pulmonary infiltration and IL-6. *Neurol Sci*. 2021;1–9. doi: 10.1007/s10072-020-04978-2

22. Planchuelo-Gómez Á, Trigo J, de Luis-García R, et al. Deep phenotyping of headache in hospitalized COVID-19 patients via principal component analysis. *Front Neurol*. 2020;11:583870. doi: 10.3389/fneur.2020.583870

23. Al-Hashel JY, Ismail II. Impact of coronavirus disease 2019 (COVID-19) pandemic on patients with migraine: a web-based survey study. *J Headache Pain*. 2020;21(1):115. doi: 0.1186/s10194-020-01183-6

24. Caronna E, Ballvé A, Llauradó A, et al. Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. *Cephalalgia*. 2020;40(13):1410–1421. doi: 10.1177/0333102420965157

25. Poncet-Megemont L, Paris P, Tronchere A, et al. High prevalence of headaches during COVID-19 infection: a retrospective cohort study. *Headache*. 2020;60(10):2578–2582. doi: 10.1111/head.13923

26. Badrah M, Riad A, Kassem I, et al. Craniofacial pain in COVID-19 patients with diabetes mellitus: Clinical and laboratory description of 21 cases. *J Med Virol*. 2021;93(5):2616–2619. doi: 10.1002/jmv.26866

https://doi.org/10.17816/clinpract71137

27. Szyszka-Sommerfeld L, Machoy M, Lipski M, Woźniak K. Electromyography as a means of assessing masticatory muscle activity in patients with pain-related temporomandibular disorders. *Pain Res Manag*. 2020;2020:9750915. doi: 10.1155/2020/9750915

28. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020;277(8):2251–2261. doi: 10.1007/s00405-020-05965-1

29. Veronese S, Sbarbati A. Chemosensory systems in COVID-19: evolution of scientific research. *ACS Chem Neurosci*. 2021;12(5):813–824. doi: 10.1021/acschemneuro.0c00788

30. Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. *J Korean Med Sci*. 2020;35(18):e174. doi: 10.3346/jkms.2020.35.e174

31. Nguyen NN, Hoang VT, Lagier JC, et al. Long-term persistence of olfactory and gustatory disorders in COVID-19 patients. *Clin Microbiol Infect*. 2021;S1198-743X(20)30781-3. doi: 10.1016/j.cmi.2020.12.021

32. Oliveira RM, Santos DH, Olivetti BC, Takahashi JT. Bilateral trochlear nerve palsy due to cerebral vasculitis related to COVID-19 infection. *Arq Neuropsiquiatr*. 2020;78(6):385–386. doi: 10.1590/0004-282X20200052

33. Doblan A, Kaplama ME, Ak S, et al. Cranial nerve involvement in COVID-19. *Am J Otolaryngol*. 2021;42(5):102999. doi: 10.1016/j.amjoto.2021.102999

34. Corrêa DG, Hygino da Cruz LC, Lopes FR, et al. Magnetic resonance imaging features of COVID-19-related cranial nerve lesions. *J Neurovirol*. 2021;27(1):171–177. doi: 10.1007/s13365-020-00934-0

35. Decavel P, Petit C, Tatu L. Tapia syndrome at the time of the COVID-19 pandemic: Lower cranial neuropathy following prolonged intubation. *Neurology*. 2020;95(7):312–313. doi: 10.1212/WNL.0000000000010011

36. Khacha A, Bouchal S, Ettabyaoui A, et al. Cavernous sinus thrombosis in a COVID-19 patient: A case report. *Radiol Case Rep*. 2021;16(3):480–482. doi: 10.1016/j.radcr.2020.12.013

37. Katyal N, Narula N, Acharya S, Govindarajan R. Neuromuscular complications with SARS-Cov-2 infection: a review. *Front Neurol*. 2020;11:1052. doi: 10.3389/fneur.2020.01052

38. Dos Santos Martins TG. Isolated post SARS-CoV-2 diplopia. *J Neurol*. 2021;268(2):391. doi: 10.1007/s00415-020-10072-6

39. Cavalagli A, Peiti G, Conti C, et al. Cranial nerves impairment in post-acute oropharyngeal dysphagia after COVID-19. *Eur J Phys Rehabil Med*. 2020;56(6):853–857. doi: 10.23736/S1973-9087.20.06452-7

40. Dicpinigaitis PV, Canning BJ. Is there (will there be) a post-COVID-19 chronic cough? *Lung*. 2020;198(6):863–865. doi: 10.1007/s00408-020-00406-6

41. Visca D, Beghè B, Fabbri LM, et al. Management of chronic refractory cough in adults. Eur J Intern Med. 2020;81:15-21. doi: 10.1016/j.ejim.2020.09.008.

42. Halpert G, Shoenfeld Y. SARS-CoV-2, the autoimmune virus. *Autoimmun Rev*. 2020;19(12):102695. doi: 10.1016/j.autrev.2020.102695

43. Abu-Rumeileh S, Abdelhak A, Foschi M, et al. Guillain-Barre syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol*. 2021;268(4):1133–1170. doi: 10.1007/s00415-020-10124-x

44. Panariello A, Bassetti R, Radice A, et al. Anti-NMDA receptor encephalitis in a psychiatric COVID-19 patient: A case report. *Brain Behav Immun*. 2020;87:179–181. doi: 10.1016/j.bbi.2020.05.054

45. Boyko AN, Sivertseva SA, Spirin NN. Lesion of the nervous system in COVID-19 infection with an emphasis on the management of patients with multiple sclerosis. *Neurology, neuropsychiatry, psychosomatics*. 2020;12(1):44–47. (In Russ). doi: 10.14412/2074-2711-2020-1S-44-47

46. Memon AB, Al-Hader R, Patel S, et al. Late-onset rapidly progressive MRI- negative-myelitis after COVID-19 illness. *Clin Neurol Neurosurg*. 2021;202:106513. doi: 10.1016/j.clin-euro.2021.106513

47. Sansone P, Giaccari LG, Aurilio C, et al. Post-Infectious Guillain-Barré syndrome related to SARS-CoV-2 infection: a systematic review. *Life (Basel)*. 2021;11(2):167. doi: 10.3390/life11020167

48. Waheed S, Bayas A, Hindi F, et al. Neurological complications of COVID-19: guillain-barre syndrome following pfizer COVID-19 vaccine. *Cureus*. 2021;13(2):e13426. doi: 10.7759/cureus.13426

49. Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barre syndrome: let's not leap to associations. *J Brain*. 2021;144(2):357–360. doi: 10.1093/brain/awaa444

50. Gusev EI, Martynov MYu, Boyko AN, et al. New coronavirus infection (COVID-19) and damage to the nervous system: mechanisms of neurological disorders, clinical manifestations, organization of neurological care. *Journal of Neurology and Psychiatry named after S.S. Korsakov*. 2020;120(6):7–16. (In Russ). doi: 10.17116/jnevro20201200617

51. Avenali M, Martinelli D, Todisco M, et al. Clinical and electrophysiological outcome measures of patients with post-infectious neurological syndromes related to COVID-19 treated with intensive neurorehabilitation. *Front Neurol*. 2021;12:643713. doi: 10.3389/fneur.2021.643713

52. Kurushina OV, Barulin AE. Damage to the central nervous system in COVID-19. *Journal of Neurology and Psychiatry named after S.S. Korsakov*. 2021;121(1):92–97. (In Russ).

53. Tung-Chen Y, Blanco-Alonso S, Antón-Huguet B, et al. Dolor torácico persistente tras resolución de la enfermedad por coronavirus 2019 (COVID-19). *Semergen*. 2020;46(Suppl 1):88–90. doi: 10.1016/j.semerg.2020.06.006

54. Yousefzai R, Bhimaraj A. Misdiagnosis in the COVID-19 era: when zebras are everywhere, don't forget the horses. *JACC Case Rep*. 2020;2(10):1614–1619. doi: 10.1016/j.jaccas.2020.04.018

55. Poggiali E, Vercelli A, Demichele E, et al. Diaphragmatic rupture and gastric perforation in a patient with COVID-19 pneumonia. *Eur J Case Rep Intern Med*. 2020;7(6):001738. doi: 10.12890/2020_001738

56. Newton-Cheh C, Zlotoff DA, Hung J, et al. Case 24-2020: a 44-year-old woman with chest pain, dyspnea, and shock. *N Engl J Med*. 2020;383(5):475–484. doi: 10.1056/NEJ-Mcpc2004975

57. Gahide G, Frandon J, Vendrell JF. COVID-19 patients presenting with afebrile acute abdominal pain. *Clin Med (Lond)*. 2020;20(3):e4–e6. doi: 10.7861/clinmed.2020-0150

58. Ivashkin VT, Sheptulin AA, Zolnikova OYu, et al. New coronavirus infection (COVID-19) and the digestive system. *Russian Journal of Gastroenterology, Hepatology and Coloproctology*. 2020;30(3):7–13. (In Russ). doi: 10.22416/1382-4376-2020-30-3-7

59. Kogan EA, Berezovsky YuS, Protsenko DD, Bagdasaryan TR. Pathological anatomy of infection caused by SARS-CoV-2. *Russian Journal of Forensic Medicine*. 2020;6(2):8–30. (In Russ). doi: 10.19048/2411-8729-2020-6-2-8-30

60. Cheung S, Quiwa JC, Pillai A, et al. Superior mesenteric artery thrombosis and acute intestinal ischemia as a consequence of COVID-19 infection. *Am J Case Rep*. 2020;21:e925753. doi: 10.12659/AJCR.925753

61. Widyadharma IP, Sari NN, Pradnyaswari KE, et al. Pain as clinical manifestations of COVID-19 infection and its management in the pandemic era: a literature review. *Egypt J Neurol Psychiatr Neurosurg*. 2020;56(1):121. doi: 10.1186/s41983-020-00258-0

62. Weng LM, Su X, Wang XQ. Pain symptoms in patients with coronavirus disease (COVID-19): a literature review. *J Pain Res*. 2021;14:147–159. doi: 10.2147/JPR.S269206

63. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *PAIN*. 2020;161(8):1694–1697. doi: 10.1097/j.pain.0000000000-001950

64. Aksan F, Nelson EA, Swedish KA. A COVID-19 patient with intense burning pain. *J Neurovirol*. 2020;26(5):800–801. doi: 10.1007/s13365-020-00887-4

65. Attal N, Martinez V, Bouhassira D. Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic. *Pain Rep*. 2021;6(1):e884. doi:10.1097/PR9.000-0000000000884

66. Meyer-Frießem CH, Gierthmühlen J, Baron R, et al. Pain during and after COVID-19 in Germany and worldwide: a narra-

tive review of current knowledge. *Pain Rep*. 2021;6(1):e893. doi: 10.1097/PR9.0000000000000893

67. Alonso-Matielo H, da Silva Oliveira VR, de Oliveira VT, Dale CS. Pain in COVID era. *Front Physiol*. 2021;12:624154. doi: 10.3389/fphys.2021.624154

68. Bureau BL, Obeidat A, Dhariwal MS, Jha P. Peripheral neuropathy as a complication of SARS-Cov-2. *Cureus*. 2020;12(11):e11452. doi: 10.7759/cureus.11452

69. Fernandez CE, Franz CK, Ko JH, et al. Imaging review of peripheral nerve injuries in patients with COVID-19. *Radiology*. 2021;298(3):E117–E130. doi: 10.1148/radiol.202020-3116

70. Andalib S, Biller J, Di Napoli M, et al. Peripheral nervous system manifestations associated with COVID-19. *Curr Neurol Neurosci Rep*. 2021;21(3):9. doi: 10.10-07/s11910-021-01102-5

71. Sabharwal P, Chakraborty S, Tyagi N, Kumar A. Acute flaccid quadriparesis in a recovering COVID-19 patient: a clinical dilemma. *Indian J Crit Care Med*. 2021;25(2):238–239. doi: 10.5005/jp-journals-10071-23728

72. Karlov VA, Burd SG, Lebedeva AV, et al. Epilepsy and COVID-19. Tactics and treatment. Recommendations of the Russian Antiepileptic League. *Epilepsy and Paroxysmal States*. 2020;12(1):84–88. (In Russ).

73. Danoun OA, Zillgitt A, Hill C, et al. Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19. *Epilepsy Behav*. 2021;118:107923. doi: 10.1016/j.yebeh.2021.107923

74. Kincaid KJ, Kung JC, Senetar AJ, et al. Post-COVID seizure: A new feature of "long-COVID". *Eur Neur Sci*. 2021;23:100340. doi: 10.1016/j.ensci.2021.100340

75. Dono F, Nucera B, Lanzone J, et al. Status epilepticus and COVID-19: A systematic review. *Epilepsy Behav*. 2021;118:107887. doi: 10.1016/j.yebeh.2021.107887

76. Belli S, Balbi B, Prince I, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived the hospitalisation. *Eur Respir J*. 2020;56(4):2002096. doi: 10.1183/13993003.02096-2020

77. Mohr A, Dannerbeck L, Lange TJ, et al. Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. *Respir Med*. 2021;16(1):732. doi: 10.4081/mrm.2021.732

78. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784. doi: 10.1371/journal.pone.0240784

79. Roy D, Ghosh R, Dubey S, et al. Neurological and neuropsychiatric impacts of COVID-19 pandemic. *Can J Neurol Sci*. 2021;48(1):9–24. doi: 10.1017/cjn.2020.173

80. Tuzun S, Keles A, Okutan D, et al. Assessment of musculoskeletal pain, fatigue and grip strength in hospitalized patients with COVID-19. *Eur J Phys Rehabil Med*. 2021. doi: 10.23736/S1973-9087.20.06563-6

81. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J Neurol Sci*. 2021;420:117271. doi: 10.1016/j.jns.2020.117271

82. Mohabbat AB, Mohabbat NM, Wight EC. Fibromyalgia and chronic fatigue syndrome in the age of COVID-19. *Mayo Clin Proc Innov Qual Outcomes*. 2020;4(6):764–766. doi: 10.1016/j.mayocpiqo.2020.08.002

83. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91–95. doi: 10.1016/j.ijid.2020.03.017

84. Ferraro F, Calafiore D, Dambruoso F, et al. COVID-19 related fatigue: Which role for rehabilitation in post-COVID-19 patients? A case series. *J Med Virol*. 2021;93(4):1896–1899. doi: 10.1002/jmv.26717

85. Miners S, Kehoe PG, Love S. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther*. 2020;12(1):170. doi: 10.1186/s13195-020-00744-w

86. Guedj E, Million M, Dudouet P, et al. (18)F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging*. 2021;48(2):592–595. doi: 10.1007/s00259-020-04973-x

87. Whiteside DM, Oleynick V, Holker E, et al. Neurocognitive deficits in severe COVID-19 infection: Case series and proposed model. *Clin Neuropsychol*. 2021;1–20. doi: 10.1080/13854046.2021.1874056

88. Stracciari A, Bottini G, Guarino M,; Cognitive and Behavioral Neurology Study Group of the Italian Neurological Society. Cognitive and behavioral manifestations in SARS-CoV-2 infection: not specific or distinctive features? *Neurol Sci*. 2021;1–9. doi: 10.1007/s10072-021-05231-0

89. Ostroumova TM, Chernousov PA, Kuznetsov IV. Cognitive disorders in patients who underwent COVID-19. *Neurology, neuropsychiatry, psychosomatics*. 2021;13(1):126–130. (In Russ). doi: 10.14412/2074-2711-2021-1-126-130

90. Alemanno F, Houdayer E, Parma A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. *PLoS One*. 2021;16(2):e0246590. doi: 10.1371/journal. pone.0246590

91. Pajo AT, Espiritu AI, Apor AD, Jamora RD. Neuropathologic findings of patients with COVID-19: a systematic review. *Neurol Sci*. 2021;1–12. doi: 10.1007/s10072-021-05068-7

92. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104–3120. doi: 10.1093/brain/awaa240

93. Strumentova ES, Lobzin VYu, Lobzin SV. Olfactory impairment, central nervous system damage and risk of neurodegenerative diseases in COVID-19. *Opinion Leader*. 2020;(8):28–34. (In Russ).

94. El Bini Dhouib I. Does coronaviruses induce neurodegenerative diseases? A systematic review on the neurotropism and neuroinvasion of SARS-CoV-2. *Drug Discov Ther*. 2021;14(6):262–272. doi: 10.5582/ddt.2020.03106

95. Steardo L, Steardo L, Verkhratsky A. Psychiatric face of COVID-19. *Transl Psychiatry*. 2020;10(1):261. doi: 10.1038/s41398-020-00949-5

96. Novikova LB, Akopyan AP, Sharapova KM, Latypova RF. Neurological and mental disorders associated with COVID 19. *Arterial Hypertension*. 2020;26(3):317–326. (In Russ). doi: 10.18705/1607-419X-2020-26-3-317-326

97. Jasti M, Nalleballe K, Dandu V, Onteddu S. A review of pathophysiology and neuropsychiatric manifestations of COVID-19. *J Neurol*. 2020;1–6. doi: 10.1007/s00415-020-09950-w

98. Rogers JP, David AS. A longer look at COVID-19 and neuropsychiatric outcomes. *Lancet Psychiatry*. 2021;8(5):351–352. doi: 10.1016/S2215-0366(21)00120-6

99. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. 2020;7(7):611–627. doi: 10.1016/S2215-0366(20)30203-0

100. Kharlamenkova NE, Bykhovets YuV, Dan MV, Nikitina DA. Experiencing uncertainty, anxiety, and anxiety in the conditions of COVID-19. *Psychological Journal*. 2020. (In Russ). URL: http://ipras.ru/cntnt/rus/institut_p/covid-19/kommentarii-eksp/har-1.html. 15.03.2021.

101. Dorozhenok IYu. Depression during the COVID-19 pandemic (analysis of clinical cases). *Neurology, neuropsychiatry, psychosomatics*. 2021;13(1):81–86. (In Russ). doi: 10.14412/2074-2711-2021-1-81-86

102. İşlek A, Balc MK. Phantosmia with COVID-19 related olfactory dysfunction: report of nine case. *Indian J Otolaryngol Head Neck Surg*. 2021;1–3. doi: 10.1007/s12070-021-02505-z

103. Liu DT, Sabha M, Damm M, et al. Parosmia is associated with relevant olfactory recovery after olfactory training. *Laryngoscope*. 2021;131(3):618–623. doi: 10.1002/lary.29277

104. Fontana IC, Bongarzone S, Gee A, et al. PET Imaging as a tool for assessing COVID-19 brain changes. *Trends Neurosci*. 2020;43(12):935–938. doi: 10.1016/ j.tins.2020.10.010

105. Al-Sarraj S, Troakes C, Hanley B, et al. Invited review: the spectrum of neuropathology in COVID-19. *Neuropathol Appl Neurobiol*. 2021;47(1):3–16. doi: 10.1111/nan.12667

https://doi.org/10.17816/clinpract71137

journal of clinical practice 2021 Vol 12 №2

106. Belli S, Balbi B, Prince I, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived the hospitalisation. *Eur Respir J*. 2020;56(4):2002096. doi: 10.1183/13993003.02096-2020

107. Goodman BP, Khoury JA, Blair JE, Grill MF. COVID-19 dysautonomia. *Front Neurol*. 2021;12:624968. doi: 10.3389/fneur.2021.624968

108. Johansson M, Stahlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the swedish experience. *JACC Case Rep*. 2021. doi: 10.1016/j.jaccas.2021.01.009

109. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res*. 2021;1–6. doi: 10.1007/s12026-021-09185-5

110. Motiejunaite J, Balagny P, Arnoult F, et al. Hyperventilation: a possible explanation for long-lasting exercise intolerance in mild COVID-19 survivors? *Front Physiol*. 2021;11:614590. doi: 10.3389/fphys.2020.614590

111. Pasquetto G, Conti GB, Susana A, et al. Syncope, Brugada syndrome, and COVID-19 lung disease. *J Arrhythm*. 2020;36(4):768–770. doi: 10.1002/joa3.12375

112. Doodnauth AV, Jallad A, Rizk D, et al. Syncope associated with sinus nodal dysfunction in a COVID-19 patient: a case report and review of the literature. *Am J Med Case Rep*. 2021;9(4):263–267. doi: 10.12691/ajmcr-9-4-15

113. Oates CP, Turagam MK, Musikantow D, et al. Syncope and presyncope in patients with COVID-19. *Pacing Clin Electrophysiol*. 2020;43(10):1139–1148. doi: 10.1111/pace.14047

114. Hernández PI, Talavera de la EB, Valle PG, García AD. Isolated syncope as a form of presentation of COVID-19 infection. *Neurologia*. 2021;36(2):185–187. doi: 10.1016/j.nrl.2020.11.001

115. Birlutiu V, Birlutiu RM, Feiereisz AI. SARS-CoV-2 infection associated with micturition syncope: Our experience with 4 case reports. *Medicine (Baltimore)*. 2020;99(31):e21512. doi: 10.1097/MD.0000000000021512

116. Singh S, Desai R, Gandhi Z, et al. Takotsubo syndrome in patients with COVID-19: a systematic review of published cases. *SN Compr Clin Med*. 2020;1–7. doi: 10.1007/s42399-020-00557-w

117. Finsterer J, Stöllberger C. SARS-CoV-2 associated polyradiculitis and myocarditis may favour Takotsubo syndrome. *Med Hypotheses*. 2021;148:110509. doi: 10.1016/j.mehy.2021. 110-509

118. Tan GP, Ho S, Fan BE, et al. Reversible platypnea-orthodeoxia in COVID-19 acute respiratory distress syndrome survivors. *Respir Physiol Neurobiol*. 2020;282:3510–3515. doi: 10.1016/j.resp.2020.103515

119. Singh K, Kadnur H, Ray A, et al. Platypnea-orthodeoxia in a patient with severe COVID-19 pneumonia. *Arch Chest Dis*. 2020;90(4). doi: 10.4081/monal-di.2020.1609

120. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *Eur Neur Sci*. 2020;21:100276. doi: 10.1016/j.ensci.2020.100276

121. Chigr F, Merzouki M, Najimi M. Autonomic brain centers and pathophysiology of COVID-19. *ACS Chem Neurosci*. 2020;11:1520–1522. doi: 10.1021/acschemneuro.0c00265

122. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond)*. 2021;21(1):e63–e67. doi: 10.7861/clinmed.2020-0896

123. Troshina EA, Melnichenko GA, Senyushkina ES, Mokrysheva NG. Adaptation of the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal systems to a new infectious disease-COVID-19 in the development of COVID-19-pneumonia and/or cytokine storm. *Clinical and Experimental Thyroidology*. 2020;16(1):21–27. (In Russ). doi: 10.14341/ket12461

124. De Gennaro R, Gastaldo E, Tamborino C, et al. Selective cranial multineuritis in severe COVID-19 pneumonia: two cases and literature review. *Neurol Sci*. 2021;42(5):1643–1648. doi: 10.1007/s10072-021-05087-4

125. Kaya Tutar N, Kale N, Tugcu B. Adie-holmes syndrome associated with COVID-19 infection: a case report. *Indian J Ophthalmol*. 2021;69(3):773–774. doi: 10.4103/ijo.IJO_3589_20

126. Alzahrani AS, Mukhtar N, Aljomaiah A, et al. The impact of COVID-19 viral infection on the hypothalamic-pituitary-adrenal axis. *Endocr Pract*. 2021;27(2):83–89. doi: 10.1016/j.eprac.2020.10.014

127. Kothandaraman N, Rengaraj A, Xue B, et al. COVID-19 endocrinopathy with hindsight from SARS. *Am J Physiol Endocrinol Metab*. 2021;320(1):E139–E150. doi: 10.1152/ajpendo.00480.2020

128. Taşlıdere B, Mehmetaj L, Özcan AB, et al. Melkersson-Rosenthal syndrome induced by COVID-19. *Am J Emerg Med*. 2021;41:262.e5–262.e7. doi: 10.1016/j.ajem.2020.08.018

129. Ahmed O, Aladham Y, Mahmood S, Abdelnaby MM. Complicated sinusitis with sphenopalatine artery thrombosis in a COVID-19 patient: a case report. *J Surg Case Rep*. 2021;2021(3):rjab010. doi: 10.1093/jscr/rjab010

130. Gherlone EF, Polizzi E, Tetè G, et al. Frequent and persistent salivary gland ectasia and oral disease after COVID-19. *J Dent Res*. 2021;100(5):464–471. doi: 10.1177/002203452-1997112

131. Katz J. Prevalence of dry mouth in COVID-19 patients with and without Sicca syndrome in a large hospital center. *Ir J Med Sci*. 2021;1–3. doi: 10.1007/s11845-020-02480-4

132. Pushkina NV. Alopecia and COVID-19. Options for the management of trichological patients. *Cosmetics and Medicine*. 2021;(1):134–140. (In Russ).

133. Meyer C, Haustrate MA, Nisolle JF, Deltombe T. Heterotopic ossification in COVID-19: a series of 4 cases. *Ann Phys Rehabil Med*. 2020;63(6):565–567. doi: 10.1016/j.rehab.2020.09.010

134. Barker-Davies RM, O'Sullivan O, Senaratne KP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. 2020;54(16):949–959. doi: 10.1136/bjsports-2020-102596

135. Putko RM, Bedrin MD, Clark DM, et al. SARS-CoV-2 and limb ischemia: a systematic review. *J Clin Orthop Trauma*. 2021;12(1):194–199. doi: 10.1016/j.jcot.2020.11.018

136. Ramondetta A, Ribero S, Costi S, Dapavo P. Pression-induced facial ulcers by prone position for COVID-19 mechanical ventilation. *Dermatol Ther*. 2020;33(4):e13748. doi:10.1111dth.13-748

137. Yu JN, Wu BB, Feng LP, Chen HL. COVID-19 related pressure injuries in patients and personnel: A systematic review. *J Tissue Viability*. 2021;S0965-206X(21)00040-1. doi: 10.1016/j.jtv.2021.04.002

138. Pauli MA, Pereira LM, Monteiro ML, et al. Painful palatal lesion in a patient with COVID-19. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2021;S2212-4403(21)00160-7. doi: 10.1016/j.oooo.2021.03.010

139. Ramani SL, Samet J, Franz CK, et al. Musculoskeletal involvement of COVID-19: review of imaging. *Skeletal Radiol*. 2021;1–11. doi: 10.1007/s00256-021-03734-7

140. Bax F, Lettieri C, Marini A, et al. Clinical and neurophysiological characterization of muscular weakness in severe COVID-19. *Neurol Sci*. 2021;1–6. doi: 10.1007/s10072-021-05110-8

141. Mehan WA, Yoon BC, Lang M, et al. Paraspinal myositis in patients with COVID-19 Infection. *AJNR Am J Neuroradiol*. 2020;41(10):1949–1952. doi: 10.3174/ajnr.A6711

142. Theodorou DJ, Theodorou SJ, Axiotis A, et al. COVID-19 vaccine-related myositis. *QJM*. 2021;hcab043. doi: 10.1093/qjmed/hcab04

143. Barp A, Velardo D, Ciscato P, et al. Anti-HMGCR myopathy misdiagnosed as motor neuron disease and complicated with COVID-19 infection. *Neurol Sci*. 2021;1–4. doi: 10.1007/s10072-021-05146-w

144. Quintana-Ortega C, Remesal A, Ruiz de Valbuena M, et al. Fatal outcome of anti-MDA5 juvenile dermatomyositis in a paediatric COVID-19 patient: a case report. *Mod Rheumatol Case Rep*. 2021;5(1):101–107. doi: 10.1080/24725625.2020.1832755

145. Nasuelli NA, Pettinaroli R, Godi L, et al. Critical illness neuromyopathy (CINM) and focal amyotrophy in intensive care unit (ICU) patients with SARS-CoV-2: a case series. *Neurol Sci*. 2021;42(3):1119–1121. doi: 10.1007/s10072-020-04820-9

146. Manzano GS, Woods JK, Amato AA. COVID-19-associated myopathy caused by type I interferonopathy. *N Engl J Med*. 2020;383(24):2389–2390. doi: 10.1056/NEJMc2031085

147. Van Aerde N, van den Berghe G, Wilmer A, et al. Intensive care unit acquired muscle weakness in COVID-19

patients. *Intensive Care Med*. 2020;46(11):2083–2085. doi: 10.1007/s00134-020-06244-7

148. Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *J Neurology*. 2020;95(15):e2109–e2118. doi: 10.12-12/WNL.0000000000010282

149. Roy D, Song J, Awad N, Zamudio P. Treatment of unexplained coma and hypokinetic-rigid syndrome in a patient with COVID-19. *BMJ Case Rep*. 2021;14(3):e239781. doi: 10.1136/bcr-2020-239781

150. Diezma-Martín AM, Morales-Casado MI, García-Alvarado N, et al. Tremor and ataxia in COVID-19. *Neurologia*. 2020;35(6):409–410. doi: 10.1016/j.nrl.2020.06.005

151. Chan JL, Murphy KA, Sarna JR. Myoclonus and cerebellar ataxia associated with COVID-19: a case report and systematic review. *J Neurol*. 2021;1–32. doi: 10.1007/s00415-021-10458-0

152. Cohen ME, Eichel R, Steiner-Birmanns B, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. *Lancet Neurol*. 2020;19(10):804–805. doi: 10.1016/S1474-4422(20)30305-7

153. Brundin P, Nath A, Beckham JD. Is COVID-19 a perfect storm for Parkinson's disease? *Trends Neurosci*. 2020;43(12):931–933. doi: 10.1016/j.tins.2020.10.009

154. Wang H, Qin R, Zhang J, Chen Y. Possible immunity, inflammation, and oxidative stress mechanisms of Alzheimer›s disease in COVID-19 patients. *Clin Neurol Neurosurg*. 2021;201:106414. doi: 10.1016/j.clineuro.2020.106414

155. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson›s disease patients affected by COVID-19. *Mov Disord*. 2020;35(6):905–908. doi: 10.1002/mds.28104

156. Vorobyov SV, Shalepo KV, Spasibova EV, et al. Infectious agents as a risk factor for the development of Alzheimer›s disease. *Journal of Infectology*. 2020;12(1):5–13. (In Russ). doi: 10.22625/2072-6732-2020-12-1-5-13

157. Yu Y, Travaglio M, Popovic R, et al. Alzheimer's and Parkinson's diseases predict different COVID-19 outcomes: a uk biobank study. *Geriatrics (Basel)*. 2021;6(1):10. doi: 10.3390/geriatrics6010010

158. Borah P, Deb PK, Chandrasekaran B, et al. Neurological consequences of SARS-CoV-2 infection and concurrence of treatment-induced neuropsychiatric adverse events in COVID-19 patients: navigating the uncharted. *Front Mol Biosci*. 2021;8:627723. doi: 10.3389/fmolb.2021.627723

159. Saniasiaya J, Kulasegarah J. Auditory cinchonism in COVID era. *Ear Nose Throat J*. 2020;99(9):597–598. doi: 10.1177/0145561320947255

160. Al-Ramadan A, Rabab'h O, Shah J, Gharaibeh A. Acute and post-acute neurological complications of COVID-19. *Neurol Int*. 2021;13(1):102–119. doi: 10.3390/neurolint13010010

161. Chang WT, Toh HS, Liao CT, Yu WL. Cardiac involvement of COVID-19: a comprehensive review. *Am J Med Sci*. 2021;361(1):14–22. doi: 10.1016/j.amjms.2020.10.002

162. See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S; Vaccination, March 2 to, 2021. *JAMA*. 2021;e217517. doi: 10.1001/jama.2021.7517

163. Wolf ME, Luz B, Niehaus L, et al. Thrombocytopenia and intracranial venous sinus thrombosis after "COVID-19 Vaccine AstraZeneca" exposure. *J Clin Med*. 2021;10(8):1599. doi: 10.3390/jcm10081599

164. Román GC, Gracia F, Torres A, et al. Acute transverse myelitis (ATM): clinical review of 43 patients with COVID-19-associated ATM and 3 post-vaccination ATM serious adverse events with the ChAdOx1 nCoV-19 vaccine (AZD1222). *Front Immunol*. 2021;12:653786. doi: 10.3389/fimmu.2021.653786

165. Waheed S, Bayas A, Hindi F, et al. Neurological complications of COVID-19: Guillain-Barre syndrome following Pfizer COVID-19 vaccine. *Cureus*. 2021;13(2):e13426. doi: 10.7759/cureus.13426

AUTHORS INFO

The author responsible for the correspondence:
Vladimir V. Belopasov, MD, Dr. Sci. (Med.), Professor; address: 121 Bakinskaya Street, Astrakhan 414000, Russia; e-mail: belopasov@yandex.ru; eLibrary SPIN: 6089-1321; ORCID: https://orcid.org/0000-0003-0458-0703

Co-authors:
Ekaterina N. Zhuravleva; e-mail: neurologKzh@rambler.ru

Natalia P. Nugmanova, MD, Cand. Sci (Med.); e-mail: nanu@ rambler.ru;

Adela T. Abdrashitova, MD, Dr. Sci. (Med.); e-mail: adelia-79@yandex.ru; eLibrary SPIN: 1820-0380

https://doi.org/10.17816/clinpract71137